REMARKS

Formal Matters

Claims 26-35 were examined. Claims 26-35 were rejected. The amendments to the claims made herein do not add new matter and are completely supported by the application as originally filed. More particularly, support for claims 26 and 28-29 directed to a targeting construct and methods of producing the targeting construct can be found, for example, at page 12, lines 33-35, at page 18, lines 22-30 and page 59, lines 18-36 through page 60, line 9 of the specification. Additionally, support for claims 30 and 32-33 directed to transgenic mice exhibiting a hypoactive phenotype and having a disruption in the melanocyte stimulating hormone receptor gene, methods of producing said transgenic mice and cells and tissues isolated from said mice may be found, for example, at page 18, lines 22-24, page 19, lines 33-35, page 21, lines 11-22, page 39, lines 28-29 and page 59, lines 18-36 through page 60, line 9 of the specification. Lastly, support for claim 35 directed to transformed cells may be found, for example, at page 2, lines 29-35 of the specification. As such, no new matter has been added.

Amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

Upon entry of the amendments, claims 26, 28-30, 32, 33 and 35 are pending in the instant application. Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Attached hereto is a marked-up version of the changes made to the pending claims by this Amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

A. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH.

Claims 26-35 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly being

non-enabling to one skilled in the art to make the invention commensurate with the scope of the claim. Specifically, the Office Action asserts that the specification, while being enabling for a homozygous melanocyte stimulating hormone receptor gene knockout mouse that **lacks production of functional melanocyte stimulating hormone receptor** protein (original emphasis), wherein said mouse exhibits hypoactivity, a method of making said mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising a melanocyte stimulating hormone receptor knockout construct, introducing said ES cells into a blastocyst, and subsequently producing a transgenic knockout mouse, does not reasonably provide enablement for a transgenic mouse comprising **any type** (emphasis added) of disrupted melanocyte stimulating hormone receptor gene, and a method of making said knockout mouse by introducing the knockout construct into, as in claim 30, **any type** (emphasis added) of cell, or, as recited in claim 31, introducing ES cells **directly** into a pseudopregnant mouse. In connection with this rejection, the Examiner states that "[t]his rejection may be overcome by amending the claims to recite only the transgenic knockout mouse that lacks production of functional melanocyte stimulating hormone receptor protein and exhibits the disclosed phenotype, and provide additional method steps in claim 31" (original emphasis). Applicants have adopted Examiner's suggested modifications, or addressed Examiner's rejection, by: (1) reciting in the pending amended claims the specific type of disrupted melanocyte stimulating hormone receptor gene (i.e., the melanocyte stimulating hormone receptor gene represented by SEQ ID NO:19, which is also referred to as the classical melanocyte stimulating hormone receptor, MSH-R, or as melanocortin receptor 1, or MC1-R); (2) reciting in claim 30 the specific type of cell (i.e., murine ES cell) into which the KO targeting construct is introduced; (3) canceling claim 31 dealing with direct introduction of ES cells into a pseudopregnant mouse; and (4) inserting language into the pending amended claims such that the transgenic mouse having a homozygous disruption in the MSH-R (MC1-R) gene "lacks production of functional protein encoded by the melanocyte stimulating hormone receptor gene and the transgenic mouse exhibits hypoactivity."

Applicants submit that pending claims 26, 28-30, 32, 33 and 35, as amended herein, are fully enabled by the teachings of the specification. As such, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

B. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH.

Claims 26-27 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. With respect to the term "selectable marker" in the above-cited claims, the Examiner recommended "to use the term 'selectable marker gene.'" Applicants have adopted Examiner's recommendation and have amended claim 26 accordingly. Regarding claim 27, the Examiner rejected such claim with respect to the language "opposite the selectable marker." Examiner's rejection of claim 27 has been rendered moot as applicants have cancelled claim 27 herein.

Applicants submit that pending amended claim 26 is definite and particularly points out and distinctly claims the subject matter regarded as the invention. As such, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

C. REJECTION UNDER 35 U.S.C. § 102(E).

Claims 26-29 and 35 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Cone et al (U.S. Pat. No. 6,278,038).

To anticipate a claim, a reference must teach every element of the claim. "A claim is anticipated [under §102] **only if each and every element as set forth in the claim is found** . . . in a single prior art reference." MPEP §2131 *citing* (Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

The Examiner asserts that the Cone reference discloses the generation of a melanocyte stimulating hormone (MSH) receptor knockout mouse by homologous recombination using a targeting construct and subsequent phenotypic analysis of the mouse. In support of this assertion, the Examiner specifically points to columns 22-30 and Examples 4 and 5 of the Cone reference.

Applicants respectfully point out that the Cone reference and, specifically the section cited by the Examiner, only discloses the generation of a knockout mouse for the MC5-R gene. As described in applicants' specification and in this Amendment, the instant invention is directed to a knockout mouse for a different and patentably distinct melanocortin receptor gene, namely

the MC1-R gene, also known as the classical MSH receptor gene (see the Cone reference at column 2, lines 57-64). While the application, as originally filed, was clear as to the specific MSH receptor gene being disrupted, applicants amend the claims herein to recite that the particular MSH receptor gene is represented by SEQ ID NO:19 (also referred to as the MC1-R gene). Moreover, while the Cone reference mentions or refers to MC1-R, such mentions and references are in a context wholly removed from the generation of knockout mice. In fact, applicants fail to find in the Cone reference even a mere suggestion of knocking out the MC1-R gene, let alone a motivation to do so. Furthermore, the Cone reference does not enable or teach how to generate knockout mice for the MC1-R gene and certainly provides no suggestion that such mice would exhibit hypoactivity.

Because the Cone reference fails to disclose the generation of MC1-R gene knockout mice (and the attendant aspects, such as the targeting construct therefor, or methods of making constructs or mice, or cells isolated therefrom), Cone fails to anticipate the claimed invention. As such, Applicants respectfully request that the rejection of pending claims 26, 28-29 and 35 under 35 U.S.C. § 102(e) as being anticipated by Cone et al (U.S. Pat. No. 6,040,138) be withdrawn.

D. REJECTION UNDER 35 U.S.C. § 103(A).

Claims 26-29 and 35 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mansour et al. (1998) *Nature* 336(24):348-352 in view of Mountjoy et al. (1992) *Science* 257:1248-1251 and Adachi et. al. (1999) *J. Immunology* 163:3363-3368.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) **must teach or suggest all the claim limitations**. MPEP §2143.

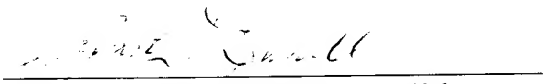
The references, either alone or combined as suggested by the Examiner, fail to teach how to generate a disruption in the specific gene of the instant invention and do not teach or suggest that MC1-R knockout mice would exhibit hypoactivity. Accordingly, the references fail to establish even a prima facie case of obviousness. As such, Applicants submit that the amended

claims are not obvious in view of the amendments and remarks set forth above. Accordingly, Applicants respectfully request that the rejection of claims 26, 28-29 and 35 under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

Applicants submit that all of the pending claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Respectfully Submitted,
DELTAGEN, INC.



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

26. (Currently Amended) A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a first portion of a melanocyte stimulating hormone receptor gene represented by SEQ ID NO:19;

(b) a second polynucleotide sequence homologous to a second portion of [a] the melanocyte stimulating hormone receptor gene; and

(c) a selectable marker gene located between the first polynucleotide sequence and the second polynucleotide sequence,

wherein the targeting construct, when introduced into a murine embryonic stem [cells] cell, results in a transgenic mouse having a disruption in [a] the melanocyte stimulating hormone receptor gene, wherein the transgenic mouse when homozygous for [a] the disruption [in a melanocyte stimulating hormone receptor gene] lacks production of functional protein encoded by the melanocyte stimulating hormone receptor gene and the transgenic mouse exhibits hypoactivity.

27. (Cancelled)

28. (Currently Amended) A method of producing a targeting construct for a melanocyte stimulating hormone receptor gene represented by SEQ ID NO: 19, the method comprising:

(a) obtaining a first polynucleotide sequence homologous to a first region of [a target] the melanocyte stimulating hormone receptor gene;

(e) obtaining a second polynucleotide sequence homologous to a second region of [a target] the melanocyte stimulating hormone receptor gene;

(f) providing a vector comprising a selectable marker; and

(g) inserting the first and second sequences into the vector to produce the targeting construct,

wherein the targeting construct, when introduced into a murine embryonic stem [cells] cell, results in a transgenic mouse having a disruption in [a] the melanocyte stimulating hormone

receptor gene, wherein the transgenic mouse when homozygous for [a] the disruption [in a melanocyte stimulating hormone receptor gene] lacks production of functional protein encoded by the melanocyte stimulating hormone receptor gene and the transgenic mouse exhibits hypoactivity.

29. (Currently Amended) A method of producing a targeting construct for a melanocyte stimulating hormone receptor gene represented by SEQ ID NO: 19, the method comprising:

(a) providing a polynucleotide sequence homologous to [a target] the melanocyte stimulating hormone receptor gene;

(b) generating two different fragments of the polynucleotide sequence;

(c) providing a vector having a gene encoding a selectable marker; and

(e) inserting the two different fragments into the vector to form the targeting construct, wherein the targeting construct, when introduced into a murine embryonic stem [cells] cell, results in a transgenic mouse having a disruption in [a] the melanocyte stimulating hormone receptor gene, wherein the transgenic mouse when homozygous for [a] the disruption [in a melanocyte stimulating hormone receptor gene] lacks production of functional protein encoded by the melanocyte stimulating hormone receptor gene and the transgenic mouse exhibits hypoactivity.

30. (Currently Amended) A method of producing a transgenic mouse comprising a homozygous disruption in a melanocyte stimulating hormone receptor gene represented by SEQ ID NO: 19, the method comprising:

(a) introducing a [melanocyte stimulating hormone receptor gene] targeting construct targeting the melanocyte stimulating hormone receptor gene into a murine embryonic stem cell;

(b) introducing the embryonic stem cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein [said] the pseudopregnant mouse gives birth to a chimeric mouse; and

(e) breeding the chimeric mouse to produce the transgenic mouse comprising a

[homozygous] disruption in [a] the melanocyte stimulating hormone receptor gene, wherein the transgenic mouse when homozygous for [a] the disruption [in a melanocyte stimulating hormone receptor gene] lacks production of functional protein encoded by the melanocyte stimulating hormone receptor gene and the transgenic mouse exhibits hypoactivity.

31. (Cancelled)

32. (Currently Amended) A transgenic mouse comprising a [homozygous] disruption in a melanocyte stimulating hormone receptor gene represented by SEQ ID NO: 19, wherein where the disruption is homozygous the transgenic mouse lacks production of functional protein encoded by the melanocyte stimulating hormone receptor gene and the transgenic mouse exhibits hypoactivity.

33. (Previously Added) A cell or tissue isolated from the transgenic mouse of claim 32.

34. (Cancelled)

35. (Currently Amended) A murine embryonic stem cell transformed with the targeting construct of claim 26[, wherein the cell comprises a disruption in a melanocyte stimulating hormone receptor gene].